

### REMARKS

This Amendment is responsive to the non-final Office Action of March 2, 2004 (Paper No. 20040226). Entry of this Amendment and reconsideration of the subject application in view thereof are respectfully requested.

#### Status of Claims

Claims 1-26 were pending in this application. Of these, claims 15-24 were withdrawn and claims 1-14, 25 and 26 stood rejected. Claims 1-9, 11-14 and 26 have been amended to clarify the invention. Claim 25 has been canceled. New claims 27-28 have been added.

Support for the new step (3) of claim 1 can be found in the specification, for example, at page 21, lines 8-20 through page and in Figure 6. Support for the new step (4) of claim 1 can be found in the specification, for example, at page 21, lines 1-11 and in Figure 6. Support for the new claims 27 and 28 can be found in the specification, for example, at page 23, lines 1-15 and in Figure 6. No new matter is added.

#### Amendments to the Specification

The specification has been amended to correct obvious typographical errors. Support for the term “[i]n each well of the reaction vessel are smaller subcells” can be found for example at page 21, lines 18-20. No new matter is added by these amendments to the specification.

#### Rejection Under 35 U.S.C. § 112

Claims 1-14 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner has asserted that in “claim 1, the final step (4) is vague and indefinite because there is no connection in the final phrase between the detection of luminescence and the detection of the mutations.” Applicant believes that entry of the amendment to claim 1 overcomes the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner has asserted that claim 6 is unclearly written. Applicant respectfully submits that it has elected to make clarifying amendments to claim 6 and believes that these

amendments overcome the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner has asserted that claim 9 lacks antecedent basis for the term "the circular DNA" and the meaning of this term is unclear. Applicant believes that entry of the amendment to claim 9 overcomes the rejection based on the lack of antecedent basis for the term "the circular DNA." Applicant respectfully disagrees to the extent the Examiner avers that the meaning of this term is unclear. Applicant submits that claim 9 explicitly recites that circular DNA is used as a template for complementary strand synthesis. Claim 9 depends from claim 1, and these claims require luminescence. One skilled in the art knows that to develop luminescence, pyrophosphate, the product of complementary DNA synthesis, is converted to ATP and reacted with chemiluminescent substrates. The specification makes clear that "the invention discloses a method for producing a large amount of pyrophosphate, a chemiluminescent substance, by using DNA strands specifically prepared for signal amplification in addition to target DNA . . . the reaction system is constructed so that a large chain of reactions of complementary strand synthesis is triggered when targets are present in a sample and acts as a template for synthesis of complementary strands. See, specification, for example, at page 5, line 14 through page 6, line 2. Further, the present specification, for example, at page 33, line 5 through page 34, line 4 expressly teaches circular DNA as a template for pyrophosphate production. Therefore, the meaning of the term "circular DNA" recited in claim 9 is clear when the claim is read in light of the specification. Accordingly, Applicant respectfully traverses the rejection, and requests its reconsideration and removal.

The Examiner has asserted that claim 25 lacks antecedent basis for "said primers." Applicant submits that this rejection is moot in light of cancellation of claim 25.

#### Rejection Under 35 U.S.C. § 102

Claims 1, 13 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ahmadian et al., 2000, Analytical Biochemistry, 280:103-110 ("Ahmadian"). Applicant respectfully traverses this rejection.

Claims 1 and 26 are independent claims. These claims are directed to a method for examining nucleotide sequences. These independent claims, as currently amended, require the use of a composition having an effective amount of at least one antisense oligonucleotide and at least one antineoplastic chemotherapeutic agent other than an antisense oligonucleotide.

Ahmadian relates to methods for typing of SNPs by pyrosequencing. Pyrosequencing is a sequencing-by-synthesis method in which a cascade of enzymatic reactions yields detectable light, which is proportional to incorporated nucleotides. In Table 1 and on page 4, Ahmadian discloses a list of primers used for PCR amplification, template preparation and pyrosequencing. Single stranded PCR products were used as templates and with annealed sequencing primers, pyrosequencing was carried out. Stepwise elongation of the primer strand upon sequential addition of the different deoxynucleoside triphosphates was carried out. In Figure 4, Ahmadian discloses raw data and predicted patterns of pyrosequencing on SNPs wiaf41 (a) and wiaf797 (b).

Anticipation requires that each and every limitation of a claim be found either expressly or inherently in a single prior art reference. *Bristol-Myers Squibb v. Ben Venue*, 246 F.3d 1368, 1374 (Fed. Cir. 2001). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible, Inc.*, 230 USPQ 81 (Fed. Cir. 1986). "Even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it is not enabling." *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985).

The Examiner contends on pages 4-5 of the Office Action that Ahmadian "teaches a method for examining nucleotide sequences" as claimed.

As a preliminary matter, Applicant respectfully points out that the Examiner's anticipation rejection discussed only the claim 1 limitations and failed out point out how Ahmadian anticipates the specific limitation in claim 26.

Applicant respectfully traverses the Examiner's contentions with respect to claim 1 and submits that Ahmadian does not teach a method as set forth in claim 1. For example, Ahmadian does not teach anything about designing DNA probes with specific sequences so that elongation of complementary strands is affected by the presence or absence of mutations in target nucleotide sequences. Ahmadian rather concerns "stepwise elongation of the primer strand upon sequential addition of the different deoxynucleoside triphosphates." See, Ahmadian at page 104, column 2, the paragraph under "*Pyrosequencing*." Ahmadian does not teach either expressly or inherently about the use of the same number of DNA probes and target sequences for elongation of complementary strands.

Notwithstanding, and solely to expedite the prosecution of the application, Applicant has made some clarifying amendments to claim 1. Ahmadian does not teach, either expressly or inherently, the step of

“immobilizing DNA probes in subcells of a reaction vessel that are compartmentalized for each said DNA probe” or

“adding the solution obtained after step (1) to the reaction vessel, wherein said DNA probes are allowed to hybridize with said target sequences or sequences complementary to said target sequences under condition that the solution can freely move among said subcells, and then the excess amount of the solution is removed so that the remaining solution can no longer freely move among said subcells.”

Thus, Ahmadian fails to teach, either expressly or inherently, each and every limitation of claim 1. Therefore, Ahmadian does not anticipate claim 1. To the extent the Examiner’s rejection applies to claim 13, this claim depends (indirectly) from claim 1. Claim 13, at least by virtue of its dependency, is similarly considered by the Applicant to patentably define itself and is novel over Ahmadian.

To the extent the Examiner wishes to apply Ahmadian against claim 26, Applicant submits that Ahmadian fails to teach a method as set forth in claim 26 as well for at least the following reasons:

Ahmadian does not disclose or teach a method having a step “wherein the first probes are immobilized in subcells of a reaction vessel that are compartmentalized for each of said probes, wherein said probes are allowed to hybridize with said target DNA under condition that the solution can freely move among said subcells; and then the excess amount of the solution is removed so that the solution can no longer freely move among said subcells.”

Ahmadian does not disclose or teach, either expressly or inherently, a method having a step of “isolating and removing excess of the first probes from said first complementary strands.”

Thus, Ahmadian fails to teach, either expressly or inherently, each and every limitation of claim 26. Therefore, Ahmadian does not anticipate claim 26.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §102 (b) are respectfully requested.

#### Rejection Under 35 U.S.C. § 103

Claims 1-10, 12, 13, 25 and 26 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ahmadian et al., 2000, Analytical Biochemistry, 280:103-110 (“Ahmadian”) in view of Barany et al., U.S. Patent 6,027,889 (“Barany”).

Claims 11 and 14 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ahmadian et al., 2000, Analytical Biochemistry, 280:103-110 ("Ahmadian") in view of Barany et al., U.S. Patent 6,027,889 ("Barany") as applied to claims 1-10, 12, 13, 25 and 26 above and further in view of Dzieglewska et al (WO 98/28440).

These rejection are respectfully traversed and believed overcome in view of the following discussion:

To establish a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *See In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. *Id*; *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

The cited combinations of references simply do not suggest invention claimed by the Applicant. Nor there is a reasonable expectation of success based on the cited combinations of references. There is nothing in the prior art as a whole to suggest the desirability, and thus the obviousness of the method claimed in, for example, claims 1 and 26.

#### A. Ahmadian and Barany

Ahmadian is discussed above. Ahmadian does not teach or suggest a method for examining nucleotide sequences as claimed by the Applicant.

Barany relates to the detection of nucleic acid sequence differences using coupled ligase detection reaction and polymerase chain reaction. Barany does not teach or suggest a method for examining nucleotide sequences as claimed by the Applicant.

The Examiner appears to be arguing that Ahmadian suggests all of the limitations of claim 1 and Barany cures the deficiency in Ahmadian and, when combined, Ahmadian and Barany references suggest each of the limitations of claims 2-10, 12, 13 and 26. Applicants disagree.

To provide a sustainable obviousness rejection, the Examiner must do more than an indiscriminate combination of Ahmadian and Barany references; the Examiner must identify some factual basis that would teach or suggest the combination of the cited references to allow an ordinarily skilled artisan to arrive at the invention set forth in claim 1-10, 12, 13 and 26. The showing of combinability must be "clear and particular." The Examiner has not met this burden.

Specifically, the Examiner has not established that Ahmadian teaches or suggests a method as set forth in claim 1. For example, the Examiner has not shown that Ahmadian teaches or suggests designing DNA probes with specific sequences so that elongation of complementary strands is affected by the presence or absence of mutations in target nucleotide sequences. Ahmadian rather concerns “stepwise elongation of the primer strand upon sequential addition of the different deoxynucleoside triphosphates.” See, Ahmadian at page 104, column 2, the paragraph under “*Pyrosequencing*.”

Further, the Examiner has not shown, for example, that Ahmadian suggests a method that uses the same number of DNA probes and target sequences for elongation of complementary strands. The Examiner has avoided this fact from the obviousness analysis.

Moreover, Ahmadian does not teach or suggest, for example, the step of “immobilizing DNA probes in subcells of a reaction vessel that are compartmentalized for each said DNA probe” or

“adding the solution obtained after step (1) to the reaction vessel, wherein said DNA probes are allowed to hybridize with said target sequences or sequences complementary to said target sequences under condition that the solution can freely move among said subcells, and then the excess amount of the solution is removed so that the remaining solution can no longer freely move among said subcells.”

With respect to claim 26, Ahmadian fails to teach or suggest a method having, for example, (i) a step “wherein the first probes are immobilized in subcells of a reaction vessel that are compartmentalized for each of said probes, wherein said probes are allowed to hybridize with said target DNA under condition that the solution can freely move among said subcells; and then the excess amount of the solution is removed so that the solution can no longer freely move among said subcells,” or (ii) a step of “isolating and removing excess of the first probes from said first complementary strands.”

Barany fails to make up for the deficiency in Ahmadian. The Examiner points to Figure 5, 11 and columns 16 and 17 of Barany. There, Barany teaches about PCR/LDR process and Allele specific LDR/PCR problem and does not teach or suggest the claim features, discussed above, missing from Ahmadian. As such, Ahmadian provides no incentive for the combination being advanced by the Examiner. Even when combined, it would not result in the present invention.

The Examiner has not established that the proposed modification or combination of Ahmadian and Barany has a reasonable expectation of success. Given the fact that Ahmadian is not about a method as set forth in claim 1 or 26, as discussed above, there is no reasonable expectation that the teachings of Ahmadian can be modified in a manner so that it will result in the claimed method for examining nucleotide sequences.

In view of the foregoing, Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness of claims 1-10, 12, 13 and 26 based on the combination of Ahmadian and Barany, under 35 U.S.C. § 103(a). Even if *prima facie* obviousness has been established, which it has not, it is urged that the cited art nonetheless fails to render the present invention obvious under a proper § 103 analysis, as the proper suggestions and motivations to combine the cited references are lacking. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

For the reasons presented above, Applicant respectfully submits that the Examiner can not establish a *prima facie* case of obviousness of dependent claim 12 under 35 U.S.C. § 103(a). As such, the rejection should now be withdrawn.

#### B. Ahmadian, Barany and Dzieglewska

Ahmadian and Barany are discussed above. Ahmadian and Barany either alone or in combination do not teach or suggest a method for examining nucleotide sequences as set forth in claim 1.

The rejected claims 11 and 14 depend, directly or indirectly, from claim 1 and require, among other things, the use of DNA with a loop structure or loop-like DNA strands.

The Examiner cites Dzieglewska for teaching loop primers and appears to argue that Dzieglewska cures the deficiencies in Barany and Ahmadian and, when combined, Ahmadian, Barany and Dzieglewska references suggest each of the limitations of claims 11 and 14. Applicants disagree.

As discussed above, Ahmadian fails to teach or suggest all the limitation of claim 1. Barany and Dzieglewska either alone or in combination do not remedy the deficiencies in the Ahmadian reference. Dzieglewska is about a method for detection of single base changes in a sample DNA but it does not teach or suggest anything about the features required by the instant claims. For example, Dzieglewska does not teach or suggest a method that uses the same number

of DNA probes and target sequences for elongation of complementary strands, a feature missing from Ahmadian or Barany. Therefore, this rejection also fails.

For the reasons presented above, Applicants respectfully submit that the Examiner can not establish a *prima facie* case of obviousness of dependent claims 11 and 14 under 35 U.S.C. § 103(a). As such, the rejection should now be withdrawn.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103 (a) are respectfully requested.

#### Newly Presented Claims 27-28

Claims 27-28 have been added to the application to recite novel features disclosed in the specification.

Applicant respectfully submits that the cited references Ahmadian, Barany and Dzieglewska do not disclose or teach the method recited in the new claims. Therefore, these references cannot anticipate the new claims. Further, Ahmadian, Barany and Dzieglewska do not teach or suggest the method as claimed herein. Therefore, these references cannot render the new claims obvious.

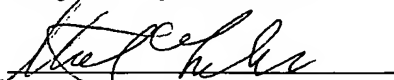
#### Conclusion

For the reasons presented above, claims 1-14 and 26-28, all the claims pending in the application, are believed by Applicant to define patentable subject matter and should be passed to issue at the earliest possible time. A Notice of Allowance is respectfully requested.



If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the present application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



Stanley P. Fisher

Registration Number 24,344

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Juan Carlos A. Marquez

Registration Number 34,072

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Nanda P.B.A. Kumar

Registration No. 44,853

**REED SMITH LLP**  
3110 Fairview Park Drive  
Suite 1400  
Falls Church, Virginia 22042  
(703) 641-4200

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